REMARKS

Claims 55-57, 59-68, 70-72, 74-88, 90-94, 102-104 and 109 were pending in this application when last examined. Claims 70-72, 74-88, 90-94, 102-104 and 109 are withdrawn from consideration. Claims 55 and 56 are currently amended and new claims 110-116 have been added.

Support for the amendments can be found in the specification and in the original claims as filed. Support can be found, for example, at page 21, line 1; at pages 27-28, Examples 3-5; and in Table 6. No new matter has been added.

INFORMATION DISCLOSURE STATEMENT

The comments regarding the IDS filed June 29, 2006 are duly noted and will be appropriately addressed in a separate filing.

CLAIM REJECTIONS - 35 USC § 112, FIRST PARAGRAPH

At page 4, the Office Action rejects claims 55-57 and 59-68 under 35 U.S.C. § 112, first paragraph, enablement requirement. Applicants respectfully traverse the rejection.

Independent claim 55 is directed to a genetically modified mouse. The mouse comprises one or more genomic Serca ATPase gene modified by inserted recombination sites. Furthermore, the recombination sites are of heterogeneous origin, and the modification is homozygous.

As stated in the MPEP, "All questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled." (MPEP 2164.08, emphasis added). Thus, a patent application is required to enable an invention only with respect to the claimed subject matter. In other words, enablement need only correspond with the scope of the claimed invention. There is no requirement that, for a patent claim to be enabled, it must enable all embodiments of the invention.

The Office Action recognizes that the specification discloses the use of inserted heterologous recombination sites to induce targeted disruptions in Serca ATPase genes in transgenic mice to generate a mouse model for heart disease. The Office Action also recognizes that claims 55-57 and 59-68 do not actually encompass any mouse model of disease. (See, page 5 of Office Action).

The Office Action appears, however, to require that the specification provide an enabling disclosure for the use of transgenic mice "to produce a mouse model of a disease." The Office Action also appears to require the specification to provide an enabling disclosure for a transgenic mouse comprising a recombinase gene that is "expressed and active during embryonic and neonatal development." The Office Action also appears to require that the specification "definitively teach the reasons for early lethality in Serca 1 negative and Serca 2 negative

mice" and "which organ(s) or tissue(s) affected by the lack of a Serca ATPase gene are the cause of death." (See, page 6 of Office Action). The Office Action then concludes that "the skilled arisan would not have been able to predict without undue experimentation whether tissue specific expression of the recombinase in any particular tissue, including heart, could avoid the lethal phenotype associated with a homozygous Serca ATPase deletion during embryonic development." (See, page 7 of Office Action).

Focusing again on the rejected claims 55-57 and 59-68, the claimed subject matter is a genetically modified mouse comprising one or more genomic Serca ATPase gene modified by inserted recombination sites, the recombination sites being of heterogeneous origin, and the modification being homozygous. The specification fully enables the scope of this subject matter. Indeed, the Office Action acknowledges that the specification enables a transgenic mouse in which both endogenous genomic copies of the SERCA2 gene contain gene contain two loxP sites flanking exons 2 and 3, and whose genome further comprises a MerCreMer transgene under transcriptional control of the α-MHC promoter. (See, bottom of page 4 to page 5 of Office Action). Thus, everything within the scope of the claims is enabled.

For at least these reasons, the specification supports the full scope of claims 55-57 and 59-68 as required by 35 U.S.C.

§ 112, first paragraph. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

CLAIM REJECTIONS - 35 USC § 112, SECOND PARAGRAPH

At page 11, the Office Action rejects claim 56 under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse the rejection.

Claim 55 defines that one or more genomic Serca ATPase gene is modified and the modification is homozygous (i.e., both copies of the Serca ATPase gene). Amended claim 56 clarifies that more than one Serca ATPase gene can be modified. One of ordinary skill in the art would recognize that a mouse contains several Serca ATPase genes (e.g., Serca1, Serca2 and Serca3, see, page 2, lines 23-30 of the present specification). Thus, several copies of a modified Serca ATPase can be present in the genetically modified mouse.

Accordingly, Applicants request reconsideration and withdrawal of the rejection.

CLAIM REJECTIONS - 35 USC § 103

At page 12, the Office Action rejects claims 55-57 and 59-68 under 35 U.S.C. § 103(a) as being unpatentable over PERIASAMY et al. (J. Biol. Chem. (1999) Vol. 274(4), 2556-2562) in view of SOHAL et al. (Circ. Res. (2001) Vol. 89, 20-25). Applicants respectfully traverse the rejection.

Present claim 55 is directed to a genetically modified mouse comprising one or more genomic Serca ATPase gene modified by inserted recombination sites, the recombination sites being of heterogeneous origin, and the modification being homozygous. Such genetically modified mice can be used, for example, to design and generate an animal model for simulating defective Ca^{2+} handling in general in adult animals and in particular for simulating heart failure. Well functioning animal systems have not previously been disclosed.

PERIASAMY investigates the function of the SERCA2 gene in heart disease by creating a SERCA2 knockout mouse. It was observed that mice with a heterozygous mutation in SERCA2, while not exhibiting heart disease, exhibited some changes in calcium uptake and blood pressure. Further, PERIASAMY highlighted that homozygous SERCA2 mutants are embryonic lethal do not survive. Thus, PERIASAMY found it necessary to perform the studies on heterozygotes (see, page 2560, discussion, 1st paragraph, lines 3-5 and 8-12).

The Office Action cites SOHAL for teaching that the embryonic, fetal, or neonatal lethality observed in some homozygous knockout mice, which prevents assessment of target gene function in the neonatal or adult heart, can be circumvented by the use of an inducible and tissue specific Cre-Lox system. The Office Action concludes that it would have been obvious to

use the system of SOHAL to generate a homozygous SERCA2 knockout mouse. Applicants respectfully disagree with this conclusion.

If a mutated gene is essential for life during the embryonic phase but is not essential for life in adult mice, then embryonic lethality observed in some homozygous knockout mice may be circumvented by using the system disclosed by SOHAL. If the gene in question is essential for life during the embryonic phase and in adult mice, however, one would assume that homozygous deletion, once induced, would be instantly lethal in adult mice. Such an animal model would serve no purpose.

SERCA2 encodes a protein, which at the time of filing of the present application, was assumed to be essential for life during the embryonic phase and in adult mice. PERIASAMY states that SERCA2, more specifically the SERCA2a isoform, plays a central role in cardiomyocyte Ca^{2+} handling (see, page 2556, left column, second paragraph) and that reduced levels of SERCA2a is a factor in heart disease (page 2562, bottom paragraph). On these grounds, PERIASAMY projected that homozygous SERCA2 mutant would not survive and that it would be necessary to perform the studies on heterozygotes (see, page 2560, discussion, first paragraph).

VER HEYEN et al. (Circ. Res. (2001) Vol. 89(9), 838-46, copy enclosed in Appendix) demonstrated that Serca2a is critical for both cardiac development and function and that the Serca2b isoform alone is not compatible with normal cardiac function.

BERS (Nature (2002) Vol. 415, 198-205, copy enclosed in Appendix) discusses the process that enables the chambers of the heart to contract and relax. In order to allow heart relaxation, Ca^{2+} must be removed from the cytosol. This is achieved by several routes, the quantitative importance of which varies between species. In mice ventricular myocytes, the SR Ca^{2+}-ATPase pump (SERCA2) removes 92% of the activator Ca^{2+}.

PERIASAMY et al. (J. Mol. Cell. Cardiol. (2001) Vol. 33, 1053-1063, copy enclosed in Appendix) teaches that there is a direct correlation between SERCA level and the contractile state of the heart and that the level of functional SERCA protein in the sarcoplasmic reticulum is one of the fundamental determinants of cardiac contractility (see, page 1057, left column, second paragraph).

SHULL (Eur. J. Biochem. FEBS (2000) Vol. 267, 5284-5290, copy enclosed in Appendix) teaches that the pump encoded by the SERCA2b gene is essential for life which is consistent with the view that SERCA2b serves an essential housekeeping function (see, page 5285, left column, second paragraph).

In view of the above reference material, one of ordinary skill in the art would expect that a homozygous SERCA2 deletion, once induced, would be instantly lethal in adult mice. Such an animal model would serve no purpose and one would be led away from producing such a genetically modified mouse as defined in the present claims. Contrary to these expected results, and as

detailed in the present specification, Applicants surprisingly found that homozygous SERCA2 deletion mutants survived for more than 50 days after induction of the deletion. Thus, the deletion mutant survival window is far wider than one of ordinary skill would have expected and renders a heart failure model possible.

For all of these reasons, PERIASAMY and SOHAL fail to teach or suggest, and would not have rendered obvious, claims 55-57 and 59-68. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

NEW CLAIMS 110-116

New claims 110-116 are directed to the mouse of claim 55, and further define the features of the mouse. New claims 110-116 are directed to the elected subject matter.

CONCLUSION

Entry of the above amendments is earnestly solicited. Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Should there be any matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized in this, concurrent, and future submissions, to charge any deficiency or credit any overpayment to Deposit Account No. 25-0120 for any

additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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APPENDIX:

- VER HEYEN et al., Circ. Res. (2001) Vol. 89(9), 838-46
- BERS, Nature (2002) Vol. 415, 198-205
- PERIASAMY et al., J. Mol. Cell. Cardiol. (2001) Vol. 33, 1053-1063
- SHULL, Eur. J. Biochem. FEBS (2000) Vol. 267, 5284-5290